REMARKS/ARGUMENTS

In response to the Office Action of July 29, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to clearly indicate that the biopolymer marker consisting of SEQ ID NO:3 evidences a link to

Alzheimer's disease. This amendment is supported by the specification as originally filed; see page 35, lines 14-18, which discloses that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer markers which evidence a link to at least one specific disease state and page 46, line 17 to page 47, line 12, identifies SEQ ID NO:3 as a biopolymer related to the specific disease, Alzheimer's disease.

Claims 39 and 44 have been amended to remove the term "isolated".

Claim 40 has been amended to provide proper antecedent basis to the term "sample" in parent claim 39.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:3 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the

decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:3 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on May 9, 2005, remains rejected under 35 USC 101 because the claimed invention is allegedly not supported by either a specific, substantial, credible or asserted utility or a well-established utility.

The Examiner states that Applicant argues that claim 1 has both a specific and a well-established utility because the specification discloses that sequences consisting of SEQ ID NO:3 are measurable in patients with Alzheimer's disease but are undetectable or regulated differently in normal patients in comparison to Alzheimer's patients. The Examiner asserts that the disclosure does not clearly correlate sequences consisting of SEQ ID NO:3 with a link to Alzheimer's disease. Specifically, the Examiner asserts that although the instant specification discloses that SEQ ID NO:3 is related to Alzheimer's disease, the asserted specific utility is not credible because Figure 1 does not exemplify differential expression of SEQ ID NO:3 and further, Band

6 is never identified as SEQ ID NO:3 so it is not proven to be differentially expressed in any of the samples.

Applicants respectfully submit that the Examiner's understanding of Applicants' argument is incorrect. No where do Applicants argue that sequences consisting of SEQ ID NO:3 are measurable in patients with Alzheimer's disease but are undetectable or regulated differently in normal patients because the claimed biopolymer marker (SEQ ID NO:3) is found in patients age-matched with the Alzheimer's disease patients and **not** found in Alzheimer's disease patients. This phenomenon can be observed in the figures (Figures 1 and 4) as originally filed and is explained at various points in the previous response filed on May 9, 2005 (see, for example, page 29 and page 35). Additionally, the instant specification as originally filed clearly indicates that the criteria for labeling a peptide a "marker" is differential expression in disease vs. normal, i.e. the definition of "marker" according to the invention is not limited to peptides found in a disease state and absent in a normal state (for example, see page 5, lines 12-20). Accordingly, it cannot be assumed that a "marker" is only found in a disease state and not found in a normal physiological state.

At page 46, line 22 to page 47, line 1, of the specification as originally filed, SEQ ID NO:3 is identified as having a

molecular weight of 1497.8025 daltons (about 1498 daltons). Figure 4 shows the characteristic profile, as obtained by mass spectrometry, of an ion of about 1498 daltons. Thus, Figure 4 shows the characteristic profile of SEQ ID NO:3. The title of the profile shown in Figure 4 (top left) indicates that the peptide(ion of 1498 daltons) was identified from the HiS 1 (scrub) gel C6. Eight bands are labeled in the HiS 1 (scrub) gel as shown in Figure 1, including Band 6 (C6) from which the claimed biopolymer marker (SEQ ID NO:3) was identified.

The gel shown in Figure 1 contains 9 samples; 4 samples obtained from Alzheimer's disease patients (lanes 1-4, as read from the left, AD-H-S-004, AD-H-S-005, AD-H-S-006 and AD-H-S-008); 4 samples obtained from patients age-matched to the Alzheimer's disease patients (lanes 5-8, AG-AD-H-S-002, AG-AD-H-S-003, AG-AD-H-S-004 and AG-AD-H-S-005) and 1 sample containing samples pooled from multiple patients determined to be normal with regard to Alzheimer's disease (lane 9). Band 6 was isolated from the sample present in lane 7; a sample which was obtained from a patient age-matched to the Alzheimer's disease patients (AG-AD-H-S-004). Band 6 was not identified in any of the samples obtained from Alzheimer's disease patients (lanes 1-4). Thus, Band 6 is differentially expressed between Alzheimer's disease and age-matched controls. The claimed biopolymer marker (SEQ ID NO:3) was

identified from Band 6, and thus, is shown to be differentially expressed between Alzheimer's disease and an age-matched physiological state. Hence, contrary to the Examiner's assertions, Band 6 is identified as SEQ ID NO:3 and is shown to differentially expressed (in age-matched vs. Alzheimer's disease) in the gel of Figure 1.

In order to illustrate this point, Applicants herein provide the attached Declaration (and figure) under 37 CFR 1.132. The figure attached to the declaration is entitled "His 1(scrub) AD vs. Age Matched AD (control)" and represents Figure 1 as originally filed. The figure was produced by scanning the original photograph of the gel. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the differential expression of the claimed biopolymer marker (SEQ ID NO:3); i.e. to clarify the presence of Band 6 (from which the claimed peptide, SEQ ID NO:3, was isolated) in samples obtained from patients age-matched to the Alzheimer's disease patients and the absence of Band 6 in samples obtained from Alzheimer's disease patients. The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

Furthermore, Applicants respectfully submit that although many

of the lanes have bands (Bands 1-8, Figure 1) in the same comparative areas, the intensity of the bands are not always identical, nor does each band necessarily correspond with only one peptide/protein.

According to the method of the invention, the criteria for evaluation is the identification of specific ions from the bands in the gel and not the appearance of the band itself; i.e. bands are selected for further analysis based on differential expression observed in gels but peptides contained within the bands are ultimately identified by mass spectrometry, and not by gel electrophoresis alone. A hypothetical example may serve to clarify. For example, a researcher has found that Band X is differentially expressed between a lung cancer patient and a patient who was determined to be normal with regard to lung cancer. In hope of identifying potential markers for lung cancer, the researcher subjects Band X to mass spectrometry and obtains three distinct mass spectral profiles. Two of these mass spectral profiles match to known proteins, Protein A and Protein B, which the researcher than identifies as potential markers for lung cancer. The fact that multiple peptides were identified from one band does not diminish the value of the peptides as markers since it is the mass spectral profile which is unique and not the band itself. If a peptide is identified in a particular band, then it is present in that band

regardless of the presence and/or absence of other peptides/proteins within the same band. Nor is differential expression limited to presence in disease and absence in normal, any differential expression can link a peptide/protein to a disease state (see page 11, lines 9-20 of the instant specification).

The Examiner states that patentability cannot be predicated upon an advantage that has not been expressly or at least implicitly, disclosed in the application as filed (*Clinical Products v. Brenner* 149 USPQ 475).

The claimed biopolymer marker (SEQ ID NO:3) is shown, in Figure 1 of the instant specification as originally filed, to be differentially expressed in patients age-matched to Alzheimer's disease patients as compared to Alzheimer's disease patients. It is acceptable in the art to refer to a differentially expressed peptide as a "marker" and thus link the peptide to the disease condition. For example, Cheng et al. (see attached abstract, Journal of Neural Transmission 103 (4):433-446 1996; reference 1) identify homovanillic acid as a useful marker for early diagnosis of Parkinson's disease since when comparing the levels of homovanillic acid in cerebrospinal fluid, they found a lower level in Parkinson's disease patients as compared with the levels found in age-matched controls.

Accordingly, Applicants expressly show differential expression

of the claimed peptide (SEQ ID NO:3) in age-matched versus Alzheimer's disease, which, in turn, links the claimed peptide (SEQ ID No:3) to Alzheimer's disease. Thus, the claimed invention is in harmony with the precedent set by *Clinical Products v. Brenner* since the differential expression (the "advantage") that is disclosed in the application as filed enables the claimed peptide (SEQ ID NO:3) to be patentable as a marker.

Applicants contend that the invention has "real-world" value. The Examiner asserts that this argument was not found persuasive because utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not substantial utilities. Apparently, the Examiner believes that Applicants' asserted utility for the instant invention requires further research in order to be deemed "substantial".

If an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant invention provides a mass spectral profile (shown in Figure 4) of a peptide which was determined to be linked to Alzheimer's disease. This mass spectral profile can be used as a reference point for testing unknown samples for the presence of the

peptide. Since the mass spectral profile is provided, no additional research is required to use the invention, (identifying the claimed SEQ ID NO:3 in sample using the disclosed mass spectral profile, Figure 4).

Alzheimer's disease most often occurs in the elderly population. Advances in diagnosis and treatment of Alzheimer's disease are highly desirable, especially since the elderly population is increasing. Thus, any advance in diagnosis and/or treatment of Alzheimer's disease would greatly benefit the elderly population which is susceptible to Alzheimer's disease. The claimed peptide (SEQ ID NO:3) represents an advance in Alzheimer's research; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, contrary to the Examiner's assertion, the instant invention has "real-world" value.

Furthermore, when considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant specification suggests that the claimed biopolymer marker (SEQ ID NO:3) is useful for diagnostics and/or therapeutics of Alzheimer's disease since it was found to be differentially expressed in Alzheimer's disease versus a normal physiological state (patients were age-matched to the Alzheimer's disease

patients and were "normal" with respect to a history of Alzheimer's disease). Applicants respectfully assert that the observed differential expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer marker (SEQ ID NO:3).

Situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a disease state versus expression in a normal physiological state.

For example, Andreasen et al. disclose a study wherein the differences in concentration of β-amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreasen et al. found that levels of CSF-β-amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF-β-amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreasen et al. Archives of Neurology 56(6):673-680 1999; reference 2).

Since the data of Andreasen et al. was available in the art at the time of the invention, one of skill in the art would be

familiar with such practice and thus likely to find that linking the observed differential expression of the claimed biopolymer marker (SEQ ID NO:3) to the suggested use of diagnostics and/or therapeutics of Alzheimer's disease is plausible.

Applicants contend that apolipoprotein E is involved in Alzheimer's disease. Therefore, one of skill in the art considering Alzheimer's disease would reasonably expect fragments of apolipoprotein E such as sequences consisting of SEQ ID NO:3 to correlate to Alzheimer's disease. The Examiner asserts that this argument is not found to be persuasive because the specific sequences claimed were not previously taught in the prior art.

Applicants respectfully submit that the references cited in the prior response filed on May 9, 2005 (Blennow et al. reference 3 and Wisniewski et al. reference 4) were not cited for the purpose of evidencing that the claimed SEQ ID NO:3 was taught in the prior art. Furthermore, Applicants respectfully contend that by requiring the prior art to disclosure the claimed sequence or by requiring a showing of a direct link between the claimed SEQ ID NO:3 and Alzheimer's disease is requiring the Applicants to meet a standard higher than that which is necessary to satisfy the utility requirement under 35 USC 101, because it has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable

doubt." Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2164.07 I C).

Applicants respectfully submit that the references (Blennow et al. reference 3 and Wisniewski et al. reference 4) were cited in the prior response as evidence to show that a person of ordinary skill in the art would be exposed to enough knowledge to conclude that the asserted utility for the claimed peptide (SEQ ID NO:3) is more likely than not true. Both references (Blennow et al. reference 3 and Wisniewski et al. reference 4) explicitly teach that apolipoprotein E is involved in the pathogenesis of Alzheimer's disease. Wisniewski et al. further teach that apolipoprotein E is associated with the formation of senile plaques (the hallmark of Alzheimer's disease) by binding to β-amyloid. Interestingly, Blennow et al. suggest that apolipoprotein E is involved in the pathogenesis of Alzheimer's disease based only upon their finding of reduced levels of apolipoprotein E in the cerebrospinal fluid of Alzheimer's disease as compared to levels in normal controls.

At page 46, line 22 to page 47, line 1 of the instant specification as originally filed, the claimed peptide (SEQ ID NO:3) is identified as a fragment of apolipoprotein E. When one of ordinary skill in the art observes that the claimed SEQ ID NO:3,

i.e. apolipoprotein E, is differentially expressed in Alzheimer's disease patients vs. age-matched patients, they would first want to know whether there is any known connection between Alzheimer's disease and apolipoprotein E. Thus, one of ordinary skill in the art would be likely to come upon the cited references in a search for an answer to this question since both of these references were available at the time of the invention. After reviewing the teachings of Blennow et al. and Wisniewski et al. one of ordinary skill in the art would find that apolipoprotein E has been explicitly implicated to be involved in the pathogenesis of Alzheimer's disease, and furthermore, a reduced level of apolipoprotein E was found in the cerebrospinal fluid of Alzheimer's disease patients and the reduced levels were enough for the researcher to associate apolipoprotein E and Alzheimer's disease. This data is in agreement with Applicants' findings of apolipoprotein E expression in patients age-matched to Alzheimer's disease patients and lack of expression in Alzheimer's disease patients. Furthermore, one of ordinary skill in the art would know that such data (differential expression) is enough to associate a peptide with a disease and thus, would not consider Applicants' assertion regarding the relationship of SEQ ID NO: 3 and Alzheimer's disease to be "far-fetched". Accordingly, it is reasonable for one of ordinary skill in the art to believe that the

claimed SEQ ID NO:3, i.e. apolipoprotein E, more likely than not is linked to Alzheimer's disease.

In conclusion, based upon all of the above arguments and attached declaration (with figure), Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:3) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on May 9, 2005, remains rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner applies many of the same arguments used to support the rejection of claim 1 under 35 USC 101 to support the instant rejection of claim 1 under 35 USC 112, first paragraph and thus, these arguments have been addressed in the above response to

the rejection of claim 1 under 35 USC 101.

Additionally, the Examiner asserts that Applicants' arguments were carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention (*In re Gardner* 166 USPQ 138).

The instant specification discloses that SEQ ID NO:3 was identified as linked to Alzheimer's disease by carrying out mass spectrometry. The mass spectral profile of SEQ ID NO:3, shown in Figure 4, is provided as a reference which can be used by those of ordinary skill in the art to identify the presence of SEQ ID NO:3 in unknown samples. Thus, Applicants respectfully submit that the instant specification meets the requirements under 35 USC 112, first paragraph by teaching how to make (identify SEQ ID NO:3 by using proteomics techniques) and use the invention (identify SEQ ID NO:3 in unknown samples in order to determine a link to Alzheimer's disease, i.e. use the invention as a marker for Alzheimer's disease).

The Examiner asserts that the prior art teaches that Alzheimer's disease has no known cure, no known cause or mechanism, and cannot be definitely assigned as a differential diagnosis in the absence of post-mortem examination and cites a reference, Patel, (Journal of Geriatric Psychiatry and Neurology 8:81-95 1995)

which allegedly supports this view.

Apparently, the Examiner has dismissed the claimed biopolymer marker (SEQ ID NO:3) as "useless" based upon what Patel is deemed to teach.

The Examiner is reminded that the purpose of the patent system is to promote the progress of science and the useful arts (see "Introduction" of the MPEP and Article 1, section 8 of the US Constitution). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote the progress of science and may discourage further medical research. The progress of science usually occurs in a "piecemeal" fashion; meaning that a "discovery" does not arise by itself but often proceeds through multiple "discoveries". For example, a new Alzheimer's drug is a "discovery" while peptide markers, such as the instant invention are smaller "discoveries". These smaller "discoveries" should be allowed patent protection because they promote the progress of science by leading to further, larger "discoveries".

Patel presents an overview of the experimental drug therapy of cognitive impairment in Alzheimer's disease as the field was in the early 1990's. In contrast with the Examiner's interpretation of Patel's teachings, Applicants contend that Patel does not teach that there is no valid means for diagnostics of Alzheimer's disease

other than post-mortem examination. Patel states at page 82, at the top of the left column:

"Over the years, many sets of diagnostic criteria for the clinical diagnosis of AD have been developed and refined, with the result that the diagnostic accuracy of AD has increased significantly. Today, the two most widely used clinical diagnostic criteria are those developed by NINCDS-ADRDA Work Group and the DSM III-R Work Group."

Thus, contrary to the Examiner's assertion, in the past years, many methods other than biopsy or post-mortem examination for diagnosing AD have been practiced and regarded as valuable; including Applicants' own patent, US 6,451,547 B1 (Jackowski et al.; reference 3) which claims methods for diagnosing Alzheimer's disease by detecting the presence of biochemical markers in bodily fluid.

The Examiner states that Applicant argues that Hampel et al. teach procedures relating a differentially expressed protein (p-tau_{231}) to a disease state and this lends support to the argument that the instant invention is enabled. The Examiner asserts that this argument was not found persuasive because Hampel et al. do not teach the instantly claimed sequence (SEQ ID NO:3) or its

correlation to Alzheimer's disease.

Applicants respectfully submit that the Examiner's understanding of Applicants' previous argument regarding the Hampel et al. reference is incorrect. No where have Applicants asserted that Hampel et al. teach the instantly claimed peptide (SEQ ID NO:3) or its correlation to Alzheimer's disease. Instead, Applicants point out that Hampel et al. disclose an experiment very similar to that of the instant inventors. Hampel et al. compared the levels of expression of a protein ($p\text{-}tau_{231}$) in a disease state (MCI, mild cognitive impairment) to the levels of expression in a normal physiological state. An elevated level of this protein ($p\text{-}tau_{231}$) was found in the MCI patients. Hampel et al. interpret the results of their experiment in a manner similar to that of the instant inventors by suggesting that an elevated level of $p\text{-}tau_{231}$ may be a predictor for the progressive cognitive decline in MCI patients which may lead to Alzheimer's disease. Hampel et al. make this suggestion without subjecting $p\text{-}tau_{231}$ to any of the "criteria" required by the Examiner when determining a marker. This comparison of the experiments of Hampel et al. to the experiments of the instant invention is made to show that it is acceptable to those practicing the art to use differential expression of a peptide/protein to associate the peptide/protein with a disease.

The Examiner asserts that Applicant contends that the

references of Tascilar et al. and Tockman et al. are not relevant to the instant invention because they do not teach SEQ ID NO:3 and its association to Alzheimer's disease. The Examiner then asserts that this argument is not found to be persuasive because the references were merely cited to show the state of the art with respect to marker discovery. A rejection is proper though a reference is not prior art when it establishes the level of ordinary skill in the art at the time of the claimed invention (see *Ex parte Erlich* 22 USPQ 2d 1463).

Applicants respectfully submit that the Examiner has incorrectly interpreted Applicants' prior argument regarding the article of Tockman et al. since nowhere in the previous response (filed on March 31, 2005) do Applicants state that they believe the Tockman et al. reference is not relevant to the instant invention because it does not teach SEQ ID NO:3 and its association to Alzheimer's disease.

However, Applicants do not disagree that Tockman et al. establishes the level of ordinary skill in the art at the time of the claimed invention. As was discussed in the previous response (filed on March 31, 2005), Applicants assert that Tockman et al. link protein markers to disease in a manner analogous to that of the instant invention.

Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer based upon expression. It does not appear that bombesin was "validated" and/or subjected to any "criteria" other than expression prior to this association. Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Thus, the teachings of Tockman et al. evidence that one of ordinary skill in the art would be inclined to link protein markers to disease prior to subjecting such markers to the extensive validation which the Examiner appears to be believe is a requirement for identification of potential biomarkers.

Accordingly, linking of the claimed SEQ ID NO:3 with Alzheimer's disease would not appear unreasonable to one of ordinary skill in the art since such linking practices were common in the art at least as far back as 1992 (year of publication of Tockman et al.) well before the time of the instant invention.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:3 between Alzheimer's disease patients and patients age matched to the Alzheimer's disease patients (determined to be normal with regard to Alzheimer's disease) evidences a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein in both the section under 35 USC 101 and the instant section. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease and would further recognize how to use the claimed biopolymer (SEQ ID NO:3)

as a marker for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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reference #1

1: J Neural Transm. 1996;103(4):433-46.

Elevated 5-S-cysteinyldopamine/homovanillic acid ratio and reduced homovanillic acid in cerebrospinal fluid: possible markers for and potential insights into the pathoetiology of Parkinson's disease.

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High-performance liquid chromatography with electrochemical detection has been employed to analyze ultrafiltrates of cerebrospinal fluid of Parkinson's Disease (PD) patients and age-matched controls for the dopamine (DA) metabolites homovanillic acid (HVA) and 5-S-cysteinyldopamine (5-S-CyS-DA). The mean level of HVA in the CSF of PD patients, measured 5 days after withdrawal from L-DOPA therapy, was significantly lower than that measured in controls. By contrast, mean levels of 5-S-CyS-DA were not significantly different in the CSF of PD patients taking L-DOPA (PD-LT patients) the same patients 5 days after discontinuing this drug (PD-LW patients) or controls. However, the mean 5-S-CyS-DA/HVA concentration ratio was significantly ($p < 0.05$) higher in the CSF of PD-LW patients compared to controls. Although the PD patient population employed in this study had been diagnosed with the disease several years previously and had been treated with L-DOPA for prolonged periods of time the results of this study suggest that low CSF levels of HVA and a high 5-S-CyS-DA/HVA ratio together might represent useful markers for early diagnosis of PD. The high 5-S-CyS-DA/HVA ratio observed in the CSF of PD-LW patients also provides support for the hypothesis that the translocation of glutathione or L-cysteine into neuromelanin-pigmented dopaminergic cell bodies in the substantia nigra might represent an early event in the pathogenesis of PD.

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2132.089 Examiner copy reference # 2

1: Arch Neurol. 1999 Jun;56(6):673-80.

Related Articles, Links

Comment in:

- Arch Neurol. 1999 Jun;56(6):655-6.

FREE TEXT AT ARCHIVES OF NEUROLOGY

Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease.

Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K.

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OBJECTIVES: To study the diagnostic potential of the 42 amino acid form of beta-amyloid (beta-amyloid(1-42)) in cerebrospinal fluid (CSF) as a biochemical marker for Alzheimer disease (AD), the intra-individual biological variation of CSF-beta-amyloid(1-42) level in patients with AD, and the possible effects of differential binding between beta-amyloid and apolipoprotein E isoforms on CSF-beta-amyloid(1-42) levels. DESIGN: A 20-month prospective follow-up study. SETTING: Community population-based sample of consecutive patients with AD referred to the Pitea River Valley Hospital, Pitea, Sweden. PATIENTS: Fifty-three patients with AD (mean +/- SD age, 71.4 +/- 7.4 years) diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria and 21 healthy, age-matched (mean +/- SD age, 68.8 +/- 8.0 years) control subjects. MAIN OUTCOME MEASURES: Cerebrospinal fluid beta-amyloid(1-42) level--analyzed using enzyme-linked immunosorbent assay--and severity of dementia--analyzed using the Mini-Mental State Examination. RESULTS: Mean +/- SD levels of CSF-beta-amyloid(1-42) were decreased (P<.001) in patients with AD (709 +/- 304 pg/mL) compared with controls (1678 +/- 436 pg/mL). Most patients with AD (49 [92%] of 53 patients) had reduced levels (<1130 pg/mL). A highly significant correlation (r = 0.90; P<.001) between baseline and 1-year follow-up CSF-beta-amyloid(1-42) levels was

found. There were no significant correlations between CSF-beta-amyloid(1-42) level and duration (r = -0.16) or severity (r = -0.02) of dementia. Low levels were also found in patients with mild dementia (Mini-Mental State Examination score, >25). CONCLUSIONS: The sensitivity of CSF-beta-amyloid(1-42) level as a diagnostic marker for AD is high. The intra-individual biological variation in CSF-beta-amyloid(1-42) level is low. Low CSF-beta-amyloid(1-42) levels are also found in the earlier stages of dementia in patients with AD. These findings suggest that CSF-beta-amyloid(1-42) analyses may be of value in the clinical diagnosis of AD, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult.

PMID: 10369305 [PubMed - indexed for MEDLINE]
